REMARKS/ARGUMENTS

The undersigned wishes to thank Examiner Romeo for granting the undersigned a telephonic interview on November 2, 2005 to advance prosecution the application.

Claims 2, 5-6, 8, 9, 11, 12, 14-38 and 53-57 are currently pending in the subject application. Applicants have amended claims 22, 54 and 55. Applicants have added claims 58 and 59. Claims 58 recites the same features as claims 2 and 53, but additionally recites a mammal afflicted with acute renal failure "arising from a pre-renal cause of acute renal failure." Claim 58 reads on all elected species. Claim 59 is similar to pending claim 20 and also reads on the elected species. Applicants submit that this amendment does not involve any issue of new matter. Applicants respectfully request entry of this amendment such that claims 2, 5-6, 8, 9, 11, 12, 14-38 and 53-59 will be pending.

Overview of Arguments

Applicants submit that the Advisory action did not consider all the arguments set forth by applicants in the communication of August 19, 2005. Applicants have identified four flaws that invalidate the rejection. The Advisory Action acknowledged the first flaw but did not fully address all of its elements. The second and third flaws were ignored. The fourth flaw was not considered in the Advisory Action as the Examiner declined to review it under 37 CFR 1.116(e).

Applicants have again set forth the four flaws in the Examiner's rejection as sections I-IV. Applicants respectfully request that to advance prosecution and to reduce issues for appeal, the Examiner fully consider each of the four flaws identified by applicants as set forth below.

Claim Rejections - 35 U.S.C. §103

The Examiner maintains its rejection of claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35-38, 53, 56 and 57 under 35 U.S.C. 103(a) as being allegedly unpatentable over Kelly (U) in view of Kubbersampath (AG) and Lefer(V). The Examiner further rejects claims 2, 15-20, 53, 54 and 55 and as being unpatentable over Kelly (U) in view of Kubbersampath (AG) and Lefer(V), and further in view of Anderson(U) and Brady (W).

I. Lack of a Reasonable Expectation of Success

MPEP 706.02(j) sets forth three basic criteria needed to establish a *prima facie* case of obviousness: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

In previous submissions, applicants have set forth ample evidence that Transforming Growth Factor Beta 1(TGFβ1), Cyclosporin A (CsA) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were known to be both (i) anti-inflammatory agents which inhibit ICAM adhesiveness and (ii) *detrimental* to renal function. One skilled in the art, then, would not have had any reasonable expectation of success for improving renal function in a subject afflicted with acute renal failure (ARF) using the alleged anti-inflammatory agent OP-1. Hence, the third requirement has not been met, and a case of *prima facie* obviousness not made.

In response, the Examiner alleged in the Final Office Action that the renal properties of OP-1 were not known at the time the application was filed, and therefore that it would be incorrect to assume that OP-1 would have an adverse effect on renal function similar to that of TGFβ1. The Examiner alleges that there is no evidence of record that OP-1 possesses any of the renal side effects of TGFβ1, CsA or NSAIDS. Therefore, evidence that TGFβ1, CsA or NSAIDS reduce renal function cannot rebut the *prima facie* case of obviousness.

Applicants acknowledge that the effects of OP-1 on renal function were not known prior to the filing of the application. But if anything this supports the novelty of the claims. Applicants discovered the usefulness of morphogens in treating ARF, in spite of the expectation that they would fail to do so by causing adverse renal effects similar to those of other anti-inflammatory agents . To support their claim that one would not have expected OP-1 to improve renal function, the Examiner is requiring applicants to do the impossible: to provide direct experimental that OP-1 has an adverse effect on renal function. This standard is illogical. If applicants discover that compound X is found to be *effective* in treating condition Y, how can they provide evidence that X is *ineffective* in treating condition Y?

Applicants cannot provide evidence that OP-1 has an adverse effect on renal function because contrary to expectation, OP-1 was found to be an effective therapeutic for ARF as set forth

in the specification. Instead, Applicants have provided evidence that other anti-inflammatory agents were known to be ineffective for improving renal function. This severely undermines the Examiner's key premise that any anti-inflammatory agent was expected to increase renal function.

Rather than applicants have to show why OP-1 would fail in treating ARF, it is the Examiner's burden to show why one skilled in the art would have expected OP-1 to be different from the other antiinflammatory agents. If at least three other classes of antiiflammatories where known to have adverse effects on renal function, why would one skilled in the art have expected OP-1 and the other morphogens be the exception? The Examiner has failed to support his premise that OP-1 would have been the exception. The Examiner alleges that in spite of the evidence showing the ineffectiveness of anti-inflammatories in treating ARF, one could not have known for sure whether OP-1 would fail in treating ARF until it was actually tested. But again, the standard is the expectation that something would work or fail, and not whether there was actual direct experimental evidence that it would fail.

The Examiner points to differences between OP-1 and TGFβ1 in bone formation to suggest that the two TGFβ-family members might have different biological properties in treating other organs. The question, however, is not whether the possibility exists, no matter how small, that two compounds can have different properties; the question is what properties one skilled in the art would have expected the morphogens to have. The Examiner has not provided any evidence why one skilled in the art would not expect OP-1 to also have adverse renal effects. He merely points out that OP-1 is a different compound than TGFβ1, CsA or an NSAID.

In summary, the Examiner has focused exclusively on OP-1's alleged anti-inflammatory property as the key attribute in making it a successful candidate for treating ARF. Applicants have proven that anti-inflammatory properties are not sufficient to treat ARF, and that in fact, many anti-inflammatory agents have detrimental effects on renal function. While having the burden of proof, the Examiner has set forth any evidence as to why one skilled in the art would have made OP-1 the exception among antiinflammatory agents. He has failed to show why one skilled in the art would have singled out OP-1 as an anti-inflammatory which *without* adverse renal effects. The Examiner merely asserts that OP-1 is a different compound than other antiinflammatory agents. But this is meaningless. All compounds have different chemical formulas from each other, but how this

observation satisfy the Examiner's burden of proof? It does not. The burden is on the Examiner to provide evidence that one would have expected OP-1 to be the exception among antiinflammatory agents and he has failed to do so. Based on the failure set forth a reasonable expectation of success, a case of *prima facie* obviousness has not been made in accordance with MPEP 706.02(j). Applicants request reconsideration and withdrawal of this ground of rejection.

II. The Examiner's Reasoning is Internally Inconsistent

The reasoning in the Final Office Action is internally inconsistent. On the one hand, the Examiner argues that properties (causing adverse renal side-effects) of one agent (TGFβ1) cannot be extrapolated to another agent (OP-1). Yet the other hand, the Examiner argues that the properties (e.g. treating renal ischemia) of one agent (an anti-ICAM antibody) can be extrapolated to another agent (OP-1). Applicants respectfully submit that the Examiner cannot use a double standard to arbitrarily choose what properties may or may not be extrapolated to suit an argument.

Similarly, the Examiner uses a double standard for determining expectation of success. The Examiner alleges based on indirect evidence, *i.e.* based on the three references cited in the 103(a) rejection, that OP-1 is expected to be effective in treating ARF. None of these references, however, provides experimental data that OP-1 improves renal function in ARF. Yet in response to applicants' assertion that data on other anti-inflammatory agents provides an expectation of *failure* for using OP-1 to treat ARF, the Examiner alleges that applicants have not provided direct evidence for OP-1 in treating ARF. The Examiner cannot demand a higher burden of proof from applicants, especially when the burden of proof for an obviousness rejection rests on the Examiner. The Examiner, therefore, must either acknowledge that his circumstantial evidence is insufficient to provide a reasonable expectation of success, or that Applicants reference to other anti-inflammatory agents is sufficient to negate such expectation.

III. References Fail to Teach or Suggest all the Claim Limitations

The combined teachings of Kelly, Kubbersampath, and Lefer also fail to teach or suggest all the elements of claims 2 and 53, and therefore cannot render these claims obvious. Applicants point out that claims 2 and 53 recite a "method of effecting an improvement in a standard marker of renal

function in said mammal" (emphasis added). Previously, Applicants noted that the Examiner incorrectly assumed that treating renal inflammation is synonymous with improving renal function, and that treating renal inflammation is sufficient to improve renal function.

In response, the Final Office Action, rather than directly addressing the failure of the references to teach this element of the claims, alleges that the references provide an expectation of success:

> Applicants argue that the references fail to teach or suggest improving a standard marker of renal function. Applicant's arguments have been considered but they are not found to be persuasive. The fact that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney, and the fact that OP-1 reduces or prevents the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, prevents or reduces the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades, disrupts the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury, and further enhances the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue, provides a reasonable expectation that administration of OP-1 to a mammal afflicted with acute renal failure would effect an improvement in a standard marker of renal function. (Emphasis added)

Clearly, "expectation of success" is not relevant to the question of whether the combination of references teach or suggest all the claim elements. Thus, the Office Action has not set forth how the references might teach or suggest all the elements of the claims, *e.g.* the improvement of a marker of renal function. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

IV. The Examiner has Failed to Examine the Elected Species *i.e.* Pre-renal Causes of ARF and Has Instead Examined Intrinsic Causes

In the Office Action of May 6, 2002, the Examiner requested a species election of causes of ARF for search purposes only, *i.e.* an election between pre-renal causes, post-renal causes and intrinsic renal causes of ARF. Applicants elected, for search purposes "pre-renal causes of acute renal failure" in the response filed on August 6, 2002. Dependent claim 20 recites several forms of pre-renal causes of ARF. Claims 21 and 22, currently withdrawn, recite forms of post-renal and

intrinsic causes, respectively.

As stated in the preceding section, the Examiner has failed to make a *prima facie* case of obviousness. Applicants submit that even if the Examiner had made a case of *prima facie* obviousness, which he has not, the case would have been for using OP-1 to treat ARF caused by renal ischemia. But renal ischemia is not a pre-renal cause of ARF. Renal ischemia is an intrinsic cause of ARF and thus is not within the elected species.

The 103(a) rejection relies, in part, on two references, Kelly and Kubbersampath, that relate to ARF caused by damage to renal tissue through ischemia or inflammation. Kelly induces renal ischemia in a mouse by clamping the renal arteries: "[u]sing a midline abdominal incision, renal arteries and veins were bilaterally occluded for 32 min with microaneurysm clamps, during which time the abdomen was closed. The time of ischemia was chosen to maximize reproducibility of renal functional impairment while minimizing animal mortality in these animals, who were not administered fluid intravenously" (see 3rd paragraph of the methods section). Similarly, as acknowledged by the Examiner on page 4, 1st paragraph in the Office Action of July 12, 2004, Kubbersampath relates to glomerulonephritis caused by unwanted inflammation and fibrosis.

Renal ischemia and glomerulonephritis are forms of *intrinsic* renal failure, not *pre-renal* causes. The 2nd paragraph of the background of the invention in the originally-filed specification states that "intrinsic causes of acute renal failure include but are not limited to infectious diseases (*e.g.* various bacterial, viral or parasitic infections) inflammatory diseases (*e.g.* glomerulonephritis, systemic lupuserythromatosus, ischemia (*e.g.* renal artery occlusion), toxic syndromes..." (emphasis added). By contrast, "pre-renal causes...do not involve direct damage to the kidneys" (same paragraph).

The classification of ischemia and glomerulonephritis in the specification as intrinsic causes of ARF is consistent with that in the art. U.S. Patent No. 5,576,287, granted 19 Nov 1996, states in the 5th paragraph in the background of the invention section that "[r]enal ischemia is one of the most common intrinsic renal causes of ARF. In general, renal ischemia refers to localized tissue hypoxia within kidneys that results from the obstruction of the inflow of blood or low blood oxygen levels" (emphasis added). Similarly, the middle part of Table 236-1 on page 1266 of Harrison's Principles of Internal Medicine, 13th Edition, McGraw Hill Co., 1994, similarly teaches that renal artery/vein

occlusion and glomerulonephritis are forms of intrinsic renal failure, and not forms of pre-renal ARF (See **Exhibit A**). Intrinsic ARF is characterized by damage to the renal tissue, which may be caused by hypoperfusion (such as by clamping of renal arteries) or by toxin damage (see page 1267, column 1, last paragraph of Harrison's).

Page 1266, 1st full paragraph of Harrison's teaches that pre-renal ARF "is due to a functional response to renal hypoperfusion and is rapidly reversible upon restoration of renal blood flow and glomerular filtration pressure." This section of Harrison's also teaches that in pre-renal ARF, renal parenchymal tissue is not damaged.

Clearly, the Examiner has failed to examine *pre-renal* causes of ARF as elected by applicants, and has instead examined the nonelected species of *intrinsic* causes of ARF.

Not only has the Examiner failed to make a proper case of *prima facie* obviousness with respect to an intrinsic case (i.e. renal ischemia), his underlying rationale for the rejection would not apply to pre-renal causes of ARF. The thrust behind the current obviousness rejection is that (i) ischemia causes inflammation and tissue damage in the kidneys, (ii) OP-1 is allegedly effective in treating inflammation and reducing tissue damage, and therefore (iii) OP-1 is expected to be effective in improving renal function. Unlike ischemia, pre-renal causes do not result in tissue damage to the kidneys as stated in both Harrison's and in the specification: "pre-renal causes...do not involve direct damage to the kidneys" (2nd paragraph of the background of the invention). In the absence of tissue damage to the kidney, why would one skilled in the art have chosen an agent that allegedly treats inflammatory tissue damage to treat a renal condition with tissue damage to the kidney? One would not have. Such an agent would be expected to be ineffective. Thus, the obviousness arguments on the record, even if they had been properly made, would not apply to the elected species of pre-renal causes of ARF.

Finally, applicants note that claim 22, which recites forms of *intrinsic* causes of ARF, has been amended to include renal artery occlusion. Support for amendment may be found on 2nd paragraph of the background of the invention. Renal artery occlusion is often used in experimental animal models to induce renal ischemia (an intrinsic cause of ARF).

Applicants respectfully request that the Examiner search the elected species of pre-renal causes of ARF. If the Examiner finds pre-renal causes to be patentable, applicants request that the

Examiner expand the search to intrinsic causes, such as renal artery occlusion, and to post-renal causes of ARF.

Conclusions

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicant believes no fee is due with this response other than the fees itemized in the accompanying fee transmittal form. If an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-514 from which the undersigned is authorized to draw.

Dated: November 15, 2005

Respectfully submitted,

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diffuses from lumen to peritubular blood. As a result, *a filtered HCO_3^- ion is reclaimed.* Secreted H^+ ions are also free to combine with non-HCO_3^- buffers (e.g., phosphate or ammonia) in the tubule fluid and are excreted in these forms in the final urine. HCO_3^-, the other original product of the breakdown of H_2CO_3, formed within the tubule cell, enters the peritubular blood, and *an HCO_3^- ion is regenerated.*

Hydrogen ions in the urine are bound primarily to filtered buffers (e.g., phosphate) in an amount (the so-called titratable acid) equivalent to the amount of alkali required to titrate the pH of the urine to the pH of blood. It is usually not possible, however, to excrete all the daily acid load as titratable acid alone. Metabolism of glutamine by proximal tubule cells to form ammonium (i.e., ammoniagenesis) serves as an additional mechanism for bicarbonate regeneration. Glutamine metabolism forms not only NH_4^+ (i.e., NH_3 plus H^+) but also HCO_3^- which is transported across the proximal tubule (HCO_3^- regeneration). The generated NH_4^+ must be excreted in urine for this process to be effective in bicarbonate regeneration. The excretion of ammonium involves secretion by proximal tubule cells (possibly on the Na:H exchanger as Na^+:NH_4^+), generation of high medullary interstitial NH_4^+ concentration by an elaborate countercurrent multiplication/exchange system, and, finally, secretion of the interstitial NH_4^+ by the collecting duct by a combination of H^+ secretion and passive NH_3 diffusion. *Ammoniagenesis* is responsive to the acid-base needs of the individual. When faced with an acute acid burden and an increased need for HCO_3^- regeneration, the rate of renal ammonia synthesis increases sharply.

The quantity of hydrogen ions excreted as titratable acid and NH_4^+ is equal to the quantity of HCO_3^- regenerated in tubule cells and added to the plasma. Under steady state conditions, the quantity of net acid excreted into the urine (the sum of titratable acid and NH_4^+ minus HCO_3^-) must equal the quantity of acid gained by the extracellular fluid from all sources. Metabolic acidosis and alkalosis result when this delicate balance is perturbed, the former the result of *insufficient* net acid excretion and the latter due to *excessive* acid excretion.

Progressive loss of renal function usually causes little or no change in arterial pH, plasma bicarbonate concentration, or arterial carbon dioxide tension (P_{CO_2}) until GFR falls below 50 percent of normal. Thereafter, all three quantities tend to decline as *metabolic acidosis* ensues. In general, the metabolic acidosis of CRF is not due to overproduction of endogenous acids but is largely a reflection of the reduction in renal mass, which limits the amount of NH_3 (and therefore HCO_3^-) that can be generated. Although surviving nephrons are probably capable of generating supernormal quantities of NH_3 *per nephron*, the diminished nephron population causes overall NH_3 production to be reduced to an extent inadequate to permit sufficient buffering of H^+ in urine. Although patients with CRF may acidify the urine normally (i.e., urine pH as low as 4.5), the defect in NH_3 production limits total daily acid excretion to 30 to 40 mmol, or one-half to two-thirds the quantity of nonvolatile acid formed in the same time period. Metabolic acidosis is the inevitable consequence of this positive balance for H^+, which in most patients with stable CRF is relatively mild and nonprogressive (arterial pH of approximately 7.33 to 7.37).

Given this substantial daily accumulation of H^+ and the typically stable and nonprogressive nature of the resulting acidosis, including the observed relative constancy of the plasma HCO_3^- concentration (albeit at reduced levels of 14 to 20 mmol/L), it follows that some large tissue source of buffering must account for the stability of the acidosis in CRF. Bone is the likely candidate, in view of its large reservoir of alkaline salts (calcium phosphate and calcium carbonate). Dissolution of this buffer source probably contributes to the osteodystrophy of CRF (see Fig. 237-1).

Although the acidosis of CRF is due to the reduction in total renal mass and is therefore tubular in origin, it nevertheless depends to a large extent on the level of GFR. When GFR is reduced to only a moderate extent (i.e., to about 50 percent of normal), retention of anions, principally sulfates and phosphates, is not pronounced, so as the plasma HCO_3^- level falls owing to tubule dysfunction, retention of Cl^- by the kidneys leads to the development of *hyperchloremic acidosis.* At this stage, therefore, *the anion gap is normal.* With further reduction in GFR and more pronounced azotemia, however, retention of phosphates, sulfates, and other *unmeasured* anions is the rule, and plasma Cl^- concentration falls to normal levels despite the reduction in plasma HCO_3^- concentration. *A moderate to large anion gap therefore develops.*

Tubule potassium transport with normal and reduced nephron mass As with H^+, the concentration of K^+ in extracellular fluid is normally maintained within a relatively narrow range, 4 to 5 mmol/L. Ninety-five percent or more of total-body K^+ is in the intracellular fluid compartment, where the intracellular concentration is approximately 160 mmol/L. Normal individuals maintain external K^+ balance by excreting into the urine an amount of K^+ per day equivalent to the amount ingested, minus the relatively small amounts lost in stool and sweat. K^+ is freely filtered at the glomerulus, although the amount excreted usually represents no more than about 20 percent of the quantity filtered. The great bulk of the filtered K^+ is *reabsorbed* in the early portions of the nephron, about two-thirds in the proximal tubule, and an additional 20 to 25 percent in the loop of Henle. A K^+ *secretory process* operates in the distal tubule and terminal nephron segments. This process is largely dependent on Na^+ reabsorption and the accompanying lumen-negative voltage creating an electrical gradient across the tubule wall, favoring K^+ secretion into the lumen of distal tubule and collecting duct.

The ability to maintain external K^+ balance and normal plasma K^+ concentration until relatively late in the course of CRF is a consequence primarily of a progressive increase in fractional excretion of K^+. Greatly enhanced rates of K^+ secretion occur in distal portions of surviving tubules. The augmented secretion rate of aldosterone contributes to enhanced tubule secretion of K^+. In addition, both the increased distal tubule flow rates in residual functioning nephrons due to the osmotic diuresis and the enhanced luminal electronegativity created by the increased concentration of highly impermeable anions such as phosphate and sulfate enhance K^+ excretion. Aldosterone also stimulates net entry of K^+ into the lumen of the colon, a mechanism known to be enhanced in CRF. More detailed discussions of the abnormalities in K^+ homeostasis in acute and chronic forms of renal failure are given in Chaps. 236 and 237.

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236 ACUTE RENAL FAILURE

HUGH R. BRADY / BARRY M. BRENNER

Acute renal failure (ARF) is characterized by rapid decline in glomerular filtration rate (hours to weeks) and retention of nitrogenous waste products. This syndrome occurs in approximately 5 percent of all hospital admissions and up to 30 percent of admissions to intensive care units. Oliguria (urine output <400 mL/d) is frequent (~50

percent) but not invariable. ARF is usually asymptomatic and is diagnosed when screening of hospitalized patients reveals a recent increase in serum blood urea nitrogen (BUN) and creatinine. ARF may complicate a wide range of diseases which for purposes of diagnosis and management are conveniently divided into three categories: (1) disorders of renal hypoperfusion in which the kidney is intrinsically normal (*prerenal azotemia, prerenal ARF*) (~55 percent), (2) diseases of the renal parenchyma (*renal azotemia, intrinsic renal ARF*) (~40 percent), and (3) acute obstruction of the urinary tract (*postrenal azotemia, postrenal ARF*) (~5 percent). Although usually reversible, ARF is a major cause of in-hospital morbidity and mortality due to the serious nature of the underlying illnesses and the high incidence of complications.

ETIOLOGY AND PATHOPHYSIOLOGY **Prerenal azotemia (prerenal ARF)** This is responsible for half of cases. This syndrome is due to a functional response to renal hypoperfusion and is rapidly reversible upon restoration of renal blood flow and glomerular ultrafiltration pressure. Renal parenchymal tissue is not damaged; indeed, kidneys from individuals with prerenal azotemia function well when transplanted into recipients with normal cardiovascular function. However, severe or prolonged hypoperfusion may lead to ischemic renal parenchymal injury and intrinsic renal azotemia. Prerenal azotemia can complicate a variety of hemodynamic disturbances, including hypovolemia, low cardiac output, systemic vasodilatation, and selective renal vasoconstriction (Table 236-1).

Intravascular volume depletion sufficient to cause ARF may result from hemorrhage (e.g., surgical, traumatic, gastrointestinal), burns, dehydration, gastrointestinal fluid losses (e.g., vomiting, diarrhea, surgical drainage), urinary tract fluid losses (e.g., drug-induced or osmotic diuresis), or sequestration of fluid in extravascular compartments (e.g., peritonitis, pancreatitis, trauma, burns, or severe hypoalbuminemia). Prerenal azotemia also may occur when *"effective" arterial blood volume* is decreased despite normal or expanded intravascular volume. "Effective" hypovolemia may complicate *low cardiac output states* (e.g., myocardial, valvular, or pericardial disease, complicated arrhythmias) and diseases characterized by *systemic vasodilatation* (e.g., sepsis, vasodilator therapy, anesthesia, anaphylaxis).

True or "effective" hypovolemia leads to a fall in mean arterial pressure that is detected as reduced stretch by arterial (e.g., carotid sinus) and cardiac baroreceptors. The latter trigger a series of neurohumoral responses designed to maintain arterial pressure. These include activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and release of vasopressin (AVP; ADH) and endothelin. Norepinephrine, angiotensin II, AVP, and endothelin cause vasoconstriction in musculocutaneous and splanchnic vascular beds, reduce salt loss through sweat glands, stimulate thirst and salt appetite, and promote renal salt and water retention. As a result, cardiac and cerebral perfusion is preserved relative to that of other "less essential" organs. Several renal responses combine to maintain glomerular perfusion and filtration in this setting. Stretch receptors in afferent arterioles, in response to a reduction in perfusion pressure, trigger relaxation of arteriolar smooth-muscle cells and vasodilatation (autoregulation). Biosynthesis of vasodilator renal prostaglandins (e.g., prostacyclin, prostaglandin E_2) and nitric oxide is also enhanced, and these compounds preferentially dilate afferent arterioles. In addition, angiotensin II induces preferential constriction of efferent arterioles, probably by virtue of the increased density of angiotensin II receptors at this location. As a result, intraglomerular pressure is preserved, and the fraction of renal plasma filtered by glomeruli (filtration fraction) is increased. During severe hypoperfusion, however, these responses prove inadequate, and ARF ensues.

Drugs that interfere with the adaptive responses may convert compensated renal hypoperfusion into overt prerenal azotemia or trigger progression of prerenal azotemia to intrinsic renal azotemia (see below). Consequently, inhibitors of renal prostaglandin biosynthesis (*cyclooxygenase inhibitors*) or of angiotensin-converting enzyme activity (*ACE inhibitors*) should be used with caution in high-renin states associated with renal vasoconstriction and hypoperfusion. ACE inhibitors should be used with special caution in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney. Under these circumstances, glomerular perfusion and filtration may be exquisitively dependent on the actions of angiotensin II. Angiotensin II preserves glomerular filtration pressure distal to stenoses by increasing systemic arterial pressure and by triggering selective constriction of efferent arterioles. ACE inhibitors blunt these responses and precipitate ARF, usually reversible, in approximately 30 percent of such patients. Indeed, while patients with renal artery stenosis are particularly prone to develop ARF following therapy with ACE inhibitors, severe systemic hypotension from any cause can compromise glomerular filtration in this setting.

TABLE 236-1 Classification and major causes of acute renal failure

PRERENAL FAILURE

- **Hypovolemia**
  - Hemorrhage, burns, dehydration
  - Gastrointestinal fluid loss: vomiting, surgical drainage, diarrhea
  - Renal fluid loss: diuretics, osmotic diuresis (e.g., diabetes mellitus), adrenal insufficiency
  - Sequestration of fluid in extravascular space: pancreatitis, peritonitis, trauma, burns, hypoalbuminemia
- **Low cardiac output**
  - Diseases of myocardium, valves, and pericardium, arrhythmias, tamponade
  - Other: pulmonary hypertension, pulmonary embolus, positive pressure mechanical ventilation
- **Increased renal systemic vascular resistance ratio**
  - Systemic vasodilatation: sepsis, antihypertensives, afterload reducers, anesthesia, anaphylaxis
  - Renal vasoconstriction: hypercalcemia, norepinephrine, epinephrine, cyclosporine, amphotericin B
  - Cirrhosis with ascites
- **Renal hypoperfusion with impairment of renal autoregulatory responses**
  - Cyclooxygenase inhibitors, angiotensin-converting enzyme inhibitors
- **Hyperviscosity syndrome (rare)**
  - Multiple myeloma, macroglobulinemia, polycythemia

INTRINSIC ACUTE RENAL FAILURE

- **Renovascular obstruction (bilateral or unilateral: one functioning kidney)**
  - Renal artery obstruction: atherosclerotic plaque, thrombosis, embolism, dissecting aneurysm, vasculitis
  - Renal vein obstruction: thrombosis, compression
- **Diseases of glomeruli or renal microvasculature**
  - Glomerulonephritis and vasculitis
  - Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, toxemia of pregnancy, accelerated hypertension, radiation nephritis, scleroderma, systemic lupus erythematosus
- **Acute tubular necrosis**
  - Ischemia: as for prerenal azotemia (hypovolemia, low cardiac output, renal vasoconstriction, systemic vasodilatation), obstetrical complications (abruptio placentae, postpartum hemorrhage)
  - Toxins: exogenous—contrast, cyclosporine, antibiotics (e.g., aminoglycosides, amphotericin B), chemotherapeutic agents (e.g., cisplatin), organic solvents (e.g., ethylene glycol), acetaminophen, illegal abortifacients; endogenous—rhabdomyolysis, hemolysis, uric acid, oxalate, plasma cell dyscrasia (e.g. myeloma)
- **Interstitial nephritis**
  - Allergic: antibiotics (e.g., beta-lactams, sulfonamides, trimethoprim, rifampin), cyclooxygenase inhibitors, diuretics, captopril
  - Infection: bacterial (e.g., acute pyelonephritis, leptospirosis), viral (e.g., CMV), fungal (e.g., candidiasis)
  - Infiltration: lymphoma, leukemia, sarcoidosis
  - Idiopathic
- **Intratubular deposition and obstruction**
  - Myeloma proteins, uric acid, oxalate, acyclovir, methotrexate, sulfonamides
- **Renal allograft rejection**

POSTRENAL FAILURE (OBSTRUCTION)

- **Ureteric**
  - Calculi, blood clot, sloughed papillae, cancer, external compression (e.g. retroperitoneal fibrosis)
- **Bladder neck**
  - Neurogenic bladder, prostatic hyperplasia, calculi, cancer, blood clot
- **Urethra**
  - Stricture, congenital valve, phimosis

Other pharmacologic agents that can induce *primary intrarenal vasoconstriction* and ARF, particularly in the setting of mild hypovolemia, include radiocontrast agents, cyclosporine, amphotericin B, epinephrine, norepinephrine, and high doses of dopamine. Hypercalcemia may compromise glomerular filtration in a similar manner. *Sepsis* due to gram-negative endotoxin-producing organisms can cause systemic vasodilatation in the presence of intense intrarenal vasoconstriction.

ARF may complicate hepatic failure (hepatorenal syndrome) due to cirrhosis or other *liver diseases*, including malignancy, hepatic resection, and biliary obstruction. Intrarenal vasoconstriction and avid sodium retention are early responses under these circumstances and may precede alterations in systemic hemodyamics. In addition, patients with liver disease complicated by portal hypertension and ascites usually have increased plasma volume but "effective" hypovolemia due to systemic vasodilatation and pooling of blood in the portal circulation. Azotemia may develop slowly as hepatic failure progresses or may be precipitated in compensated patients by hemodynamic insults such as hemorrhage, paracentesis, or administration of diuretics, vasodilators, or cyclooxygenase inhibitors. ARF may progress relentlessly in hepatic failure even in the presence of satisfactory plasma volume and blood pressure, possibly as a result of ongoing intrarenal vasoconstriction, hypoperfusion, and ischemia. It must be remembered, however, that patients with liver disease also can develop other forms of ARF (e.g., sepsis, nephrotoxic medications) and that a diagnosis of hepatorenal syndrome should be made only after exclusion of other causes.

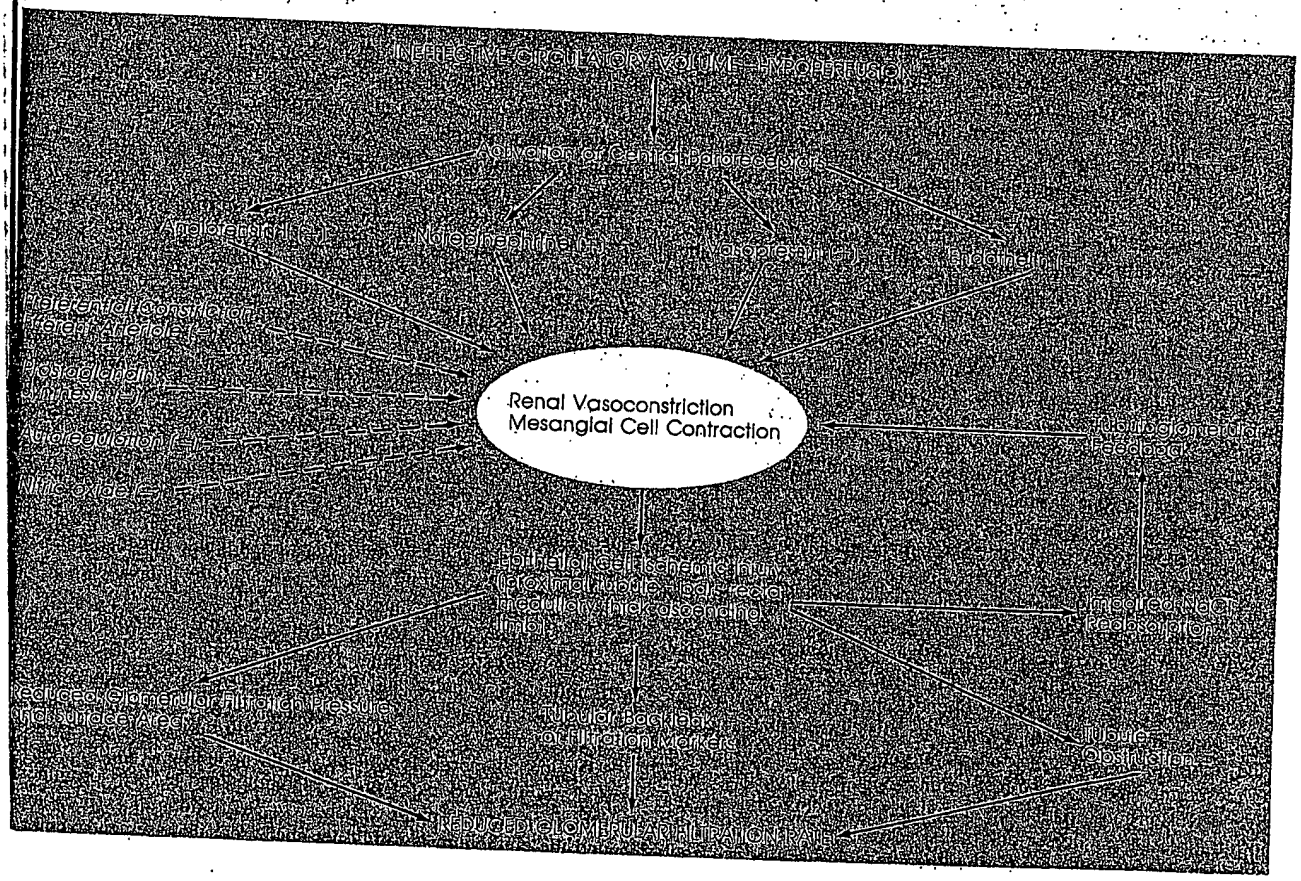
Intrinsic renal azotemia (intrinsic renal ARF) This can complicate many disorders that affect the renal parenchyma (see Table 236-1). Most cases are caused either by ischemia secondary to renal hypoperfusion (ischemic ARF) or toxins (nephrotoxic ARF). Since ischemic and nephrotoxic ARF are frequently associated with necrosis of tubule epithelial cells, this syndrome is often referred to as *acute tubular necrosis* (ATN). Unfortunately, the terms *intrinsic renal ARF* and *ATN* are often used interchangeably, but this is inappropriate because some parenchymal diseases (e.g., vasculitis, glomerulonephritis; interstitial nephritis) can cause ARF without tubule cell necrosis. Furthermore, the pathologic term *ATN* is frequently inaccurate even in ischemic or nephrotoxic ARF because tubule cell necrosis may not be present in >20 to 30 percent of cases.

ISCHEMIC ARF As noted above, prerenal azotemia and ischemic ARF can represent a spectrum of the same disease. They differ in that ischemic ARF, in contrast to prerenal azotemia, does not resolve rapidly upon restoration of normal renal perfusion. Renal hypoperfusion from any cause (see Table 236-1) may lead to ischemic ARF if severe enough to overwhelm renal autoregulatory and neurohumoral defense mechanisms (see above). Ischemic ARF occurs most frequently after cardiovascular surgery, trauma, hemorrhage, sepsis, or dehydration. This syndrome also may complicate mild forms of true or "effective" hypovolemia, particularly in patients receiving cyclooxygenase or ACE inhibitors or with renovascular disease.

Postulated mechanisms by which renal hypoperfusion and ischemia impair glomerular filtration include (1) reduction in glomerular perfusion and filtration (previously called *vasomotor nephropathy*), (2) obstruction of urine flow in tubules by cells and debris (including casts) derived from ischemic tubule epithelium, and (3) backleak of glomerular filtrate through ischemic tubule epithelium (Fig. 236-1). In addition, neutrophil activation within the renal vasculature and neutrophil-mediated cell injury may contribute.

Glomerular filtration is flow-dependent, and intrarenal vasoconstriction impairs GFR and compromises renal oxygenation. Ischemia of renal endothelial cells may cause a sustained fall in renal blood flow, glomerular ultrafiltration pressure, and surface area by blocking production of endothelial cell–derived vasodilators (e.g., nitric oxide, prostacyclin) and/or release of endothelial cell–derived vasoconstric-

FIGURE 236-1 Proposed pathophysiology of ischemic acute renal failure.



tors (e.g., endothelin). Renal hypoperfusion leads to ischemia of renal tubule cells, particularly the terminal straight portion of proximal tubules (pars recta) and the thick ascending limb of the loop of Henle. These segments traverse the corticomedullary junction and outer medulla, regions of the kidney that are relatively hypoxic compared with the renal cortex, even in health, because of the unique countercurrent arrangement of the vasculature. Furthermore, proximal tubules and thick ascending limb cells have greater oxygen requirements than other renal cells because of high rates of active (ATP-dependent) sodium transport. Proximal tubule cells may be prone to ischemic injury because they rely exclusively on mitochondrial oxidative phosphorylation (oxygen-dependent) for ATP synthesis and cannot generate ATP from anerobic glycolysis. Cellular ischemia causes alterations in energetics, ion transport, and membrane integrity that ultimately lead to cell necrosis. These include depletion of ATP, inhibition of active transport of sodium and other solutes, impairment of cell volume regulation and cell swelling, cytoskeletal disruption, accumulation of intracellular calcium, altered phospholipid metabolism, free radical formation, and peroxidation of membrane lipids. While epithelial cell function is impaired during ischemia, free radical–mediated injury may be most severe during reperfusion and reoxygenation. Necrotic tubule epithelium may permit backleak of filtered solutes, including creatinine, urea, and other nitrogenous waste products, thus rendering glomerular filtration ineffective. In addition, necrotic tubule cells may slough into tubule lumens, obstruct urine flow, increase intratubular pressure, and impair further formation of glomerular filtrate.

Epithelial cell injury per se causes secondary intrarenal vasoconstriction by a process termed *tubuloglomerular feedback*. Specialized epithelial cells in the macula densa region of distal tubules detect increases in distal salt (probably chloride) delivery due to impaired reabsorption by proximal nephron segments and in turn stimulate constriction of adjacent afferent arterioles and further compromise glomerular perfusion and filtration.

NEPHROTOXIC ARF This may complicate administration of diverse pharmacologic agents (see Table 236-1). In addition, endogenously generated compounds may lead to ARF at high concentrations. The kidney is particularly susceptible to nephrotoxic injury by virtue of its rich blood supply (25 percent of cardiac output) and ability to concentrate toxins in the medullary interstitium (via the renal countercurrent mechanism) and renal epithelial cells (via specific transporters). ARF complicates 10 to 30 percent of courses of *aminoglycoside antibiotics* and up to 70 percent of courses of the chemotherapeutic agent *cisplatin*. Aminoglycosides are filtered across the glomerular filtration barrier and accumulated by proximal tubule cells after interaction with phospholipid residues on brush border membranes. Aminoglycosides appear to disrupt normal processing of membrane phospholipids by lysosomes. Cisplatin is also accumulated by proximal tubule cells and causes mitochondrial injury, inhibition of ATPase activity and solute transport, and free radical injury to cell membranes. In addition, both agents cause renal vasoconstriction, probably as a consequence of tubuloglomerular feedback (see above). ARF due to aminoglycosides and cisplatin is usually nonoliguric due, in part, to associated impairment of urinary concentrating mechanisms.

Acute intrarenal vasoconstriction contributes to the ARF due to *radiocontrast agents* (contrast nephropathy) and *cyclosporine*. Mild contrast nephropathy is characterized by an acute decline in GFR, a benign urine sediment, and a low fractional excretion of sodium and thus resembles prerenal azotemia; however, severe cases may show tubule cell injury. Ionic high-osmolality and nonionic low-osmolality contrast agents are equally toxic in this regard. Postulated mechanisms include intrarenal vasoconstriction and ischemia, possibly triggered by endothelin release from endothelial cells, direct tubular toxicity, and intraluminal precipitation of protein or uric acid crystals. Cyclosporine appears to provoke intrarenal vasoconstriction and hypoperfusion and stimulate mesangial cell contraction and a decrease in filtration surface area. Frank tubule necrosis is rare in this setting, although long-term cyclosporine therapy may cause irreversible renal impairment as a consequence of chronic medullary ischemia. *Amphotericin* causes dose-related ARF by inducing intense renal vasoconstriction and via direct toxicity to proximal and distal tubule cells. Chronic renal failure, hypovolemia, concomitant exposure to other toxins, and old age predispose patients to most forms of nephrotoxic injury. In addition, diabetes mellitus and multiple myeloma are risk factors for acute contrast agent nephropathy.

Rhabdomyolysis and *hemolysis* can cause ARF, particularly in hypovolemic or acidotic individuals. Rhabdomyolysis and myoglobinuric ARF may occur with traumatic crush injury, muscle ischemia (e.g., arterial insufficiency, muscle compression, cocaine overdose), seizures, excessive exercise, heat stroke or malignant hyperthermia, alcoholism, and infectious (e.g., influenza, legionella) or metabolic disorders (e.g., hypokalemia, hypophosphatemia, or myophosphorylase or phosphofructokinase deficiency). ARF due to hemolysis is seen most commonly following blood transfusion reactions. The mechanisms by which rhabdomyolysis and hemolysis impair GFR are unclear, since neither hemoglobin nor myoglobin is nephrotoxic when injected into laboratory animals. Myoglobin and hemoglobin or other compounds released from muscle or red blood cells may cause ARF via direct toxic effects on tubule epithelial cells or by inducing intratubular cast formation. Hypovolemia or acidosis may contribute to ARF in this setting by promoting intranephronal cast formation. In addition, hemoglobin and myoglobin inhibit nitric oxide and may trigger intrarenal vasoconstriction and ischemia in patients with borderline renal hypoperfusion.

Intratubular obstruction may play an important role in ARF in several diseases. Casts containing filtered immunoglobulin light chains and other urine proteins, including Tamm-Horsfall protein produced by thick ascending limb cells, may cause ARF in patients with plasma cell dyscrasias (myeloma-cast nephropathy). High urine salt concentrations and low urine pH appear to promote this process. However, the correlation between cast formation and renal insufficiency is poor in myeloma, suggesting that light chains may be toxic to tubule epithelial cells. Intratubular obstruction also may cause ARF in patients with severe *hyperuricosuria* or *hyperoxaluria* or in those receiving intravenous *methotrexate*, *acyclovir*, *dextrans*, or *sulfonamide antibiotics*. Acute uric acid nephropathy typically complicates treatment of lymphoproliferative or myeloproliferative disorders but may occur in other forms of primary or secondary hyperuricemia if the urine is concentrated. Acute uric acid nephropathy is rare when plasma concentrations are less than 900 to 1200 μmol/L (15 to 20 mg/dL). Oxalate-induced ARF usually occurs as a complication of ethylene glycol toxicity but may occur in primary hyperoxaluria or in other secondary forms of hyperoxaluria (e.g., malabsorption, massive vitamin C ingestion, methoxyflurane anesthesia).

PATHOLOGY OF ARF The characteristic finding in ischemic ARF is focal necrosis of tubule epithelium and occlusion of tubule lumens with casts of intact or degenerating epithelial cells, cellular debris, Tamm-Horsfall mucoprotein, and pigments. However, the spectrum of pathology includes apparently intact epithelium, detachment of epithelial cells from their basement membranes without necrosis, mild epithelial cell swelling, disruption of luminal brush border membranes, and frank epithelial cell necrosis. While any nephron segment may be involved, necrosis is most severe in the straight portion (pars recta) of proximal tubules and in the medullary thick ascending limb of Henle. Other changes include dilatation of tubule lumens, presumably due to increased intratubular pressure, inflammation and edema of the renal interstitium, and areas of tubule regeneration. Leukocytes may accumulate in the vasa recta; the glomeruli and renal vasculature are characteristically normal. Bilateral cortical necrosis with destruction of both tubules and glomeruli may occasionally complicate massive hemorrhage or prolonged hypotension.

The pathology of nephrotoxic ARF differs from that in ischemic ARF in that morphologic changes are common in both convoluted and straight portions of proximal tubules and are less prominent in other segments. Tubule cell necrosis tends to be less pronounced, and the epithelium is rarely detached from its basement membrane.

Indeed, renal biopsy specimens may be normal in nephrotoxic ARF even in the presence of epithelial cell dysfunction. Proximal tubule myeloid bodies, characteristic, albeit nonspecific, findings in aminoglycoside-induced ARF, are electron-dense lamellar structures that reflect accumulation of cell membrane phospholipids in lysosomes and likely result from abnormal intracellular phospholipid processing. Their role in the pathogenesis of aminoglycoside nephrotoxicity is uncertain.

COURSE OF ISCHEMIC AND NEPHROTOXIC ARF Most cases of ischemic or nephrotoxic ARF are characterized by three distinct phases. The *initiation phase* is the period from initial exposure to the causative insult to development of established ARF. Restoration of renal perfusion or elimination of nephrotoxins during this phase may reverse or limit the renal injury. The early initiation phase is usually identified retrospectively, since serum creatinine does not rise until GFR is reduced by 40 percent or more. In milder renal injury, the decline in GFR is counterbalanced by an increase in creatinine secretion into the tubule lumen. During the *maintenance phase* (average 7 to 14 days), the GFR is depressed, and metabolic consequences of ARF may develop. A *recovery phase* in most patients is characterized by tubule cell regeneration and a gradual return of GFR to or toward normal. The recovery phase may be complicated by diuresis (*diuretic phase*) due to excretion of retained salt and water and other solutes, continued use of diuretics, and/or delayed recovery of epithelial cell function (solute and water reabsorption) relative to glomerular filtration.

INTRINSIC RENAL AZOTEMIA FROM OTHER CAUSES Other diseases of the renal vasculature, glomeruli, and interstitium may lead to ARF (see Table 236-1). Acute obstruction of renal arteries or veins (e.g., thrombosis) may cause an abrupt decline in GFR if bilateral or if unilateral in patients with a solitary functioning kidney. Patients with advanced atherosclerosis may develop ARF spontaneously, following trauma, or after manipulation of the aorta or renal arteries due to embolization of cholesterol crystals to the renal vasculature. Cholesterol crystals lodge in small and medium-sized arteries and incite a giant cell and fibrotic reaction in the vessel wall with narrowing or obstruction of the lumen. Atheroembolic ARF is usually irreversible. Other diseases of the renal microvasculature that may cause intrinsic renal azotemia include acute glomerulonephritis and vasculitis, hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), malignant hypertension, toxemia of pregnancy, scleroderma, and radiation injury. These disorders are characterized by either immune or physical injury to vessel walls, thrombotic microangiopathy, or both. Occlusion of renal arteries, arterioles, or glomerular capillaries leads to glomerular hypoperfusion and a fall in GFR. Pharmacologic agents may cause ARF by triggering allergic interstitial nephritis, characterized by infiltration of the interstitial space by macrophages, lymphocytes, plasma cells, polymorphonuclear leukocytes, and other inflammatory cells and interstitial edema. Common causes of allergic interstitial nephritis include antibiotics (e.g., penicillins, cephalosporins, trimethoprim, sulfonamides, rifampicin), nonsteroidal anti-inflammatory drugs, captopril, and diuretics (see Table 236-1). Occasionally, ARF may complicate interstitial nephritis due to infections, neoplasia, or infiltrative processes.

Pregnancy is associated with an increased risk of ARF, although the incidence has decreased with improvements in obstetric care. Azotemia is usually triggered by ischemic (e.g., abruptio placentae, postpartum hemorrhage) or nephrotoxic (illegal abortifacients) renal injury or toxemia of pregnancy. In addition, the postpartum period may be complicated by ARF and thrombotic microangiopathy.

Postrenal azotemia Urinary tract obstruction accounts for approximately 5 percent of ARF. Since one kidney has sufficient clearance capacity to excrete nitrogenous waste products, ARF from obstruction either requires obstruction between the external urethral meatus and bladder neck, bilateral ureter obstruction, or unilateral ureter obstruction in a patient with one functioning kidney. Bladder neck obstruction is the most common cause and may be due to prostatic disease (e.g., hyperplasia, neoplasia, or infection), neurogenic bladder, or anticholinergic drugs. Less common causes include blood clots, calculi, and urethritis with spasm. Ureteric obstruction may result from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia or abscess, inadvertent surgical ligature). During the early stages of obstruction (hours to days), continued glomerular filtration leads to increased intraluminal pressure upstream to the obstruction, eventuating in gradual distension of proximal ureter, renal pelvis, and calyces and a fall in GFR. While acute obstruction may cause an initial increase in renal blood flow, arteriolar vasoconstriction supervenes and leads to a further decline in glomerular filtration.

CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS Patients with azotemia should be assessed to determine if renal failure is acute or chronic. An acute process is established if review of laboratory records reveals a recent rise in BUN and serum creatinine, but previous measurements are usually not available. Findings that suggest chronic renal failure include anemia, neuropathy, and radiologic evidence of renal osteodystrophy or small scarred kidneys (see Chap. 237). However, anemia also may complicate ARF (see below), and renal size may be normal or increased in chronic renal disease (e.g., diabetic nephropathy, amyloid, polycystic kidney disease). Once a diagnosis of ARF is established, appropriate management relies on elucidation of the cause of ARF and requires careful clinical assessment, including review of presenting symptoms, drug history and hospital course, physical examination and urinalysis, appropriate laboratory tests and renal imaging techniques, and occasional renal biopsy.

Clinical assessment *Prerenal azotemia* should be suspected in patients suffering an elevation in serum creatinine following hemorrhage, excessive gastrointestinal or urinary fluid loss, or extensive burns, particularly if access to fluids is restricted (e.g., as in comatose or obtunded patients or those on mechanical ventilation). Supportive evidence includes thirst, orthostatic hypotension and tachycardia, reduced jugular venous pressure, decreased skin turgor, dry mucous membranes, and reduced axillary sweating. Nursing and pharmacy records should be reviewed for evidence of a decline in urine output and body weight and recent use of cyclooxygenase or ACE inhibitors. Clinical examination may reveal stigmata of chronic liver disease and portal hypertension (e.g., palmar erythema, jaundice, telangiectasia, caput medusae, splenomegaly, ascites), cardiac failure (e.g., peripheral edema, hepatic congestion, elevated jugular venous pressure, bibasilar lung crackles, gallop rhythm, cold extremities), or other causes of "effective" hypovolemia (see Table 236-1). Invasive hemodynamic monitoring (central venous and/or Swan-Ganz catheterization) may be necessary in complicated cases. Definitive diagnosis of prerenal azotemia can only be made when restoration of renal perfusion results in prompt resolution of ARF.

Intrinsic renal azotemia due to ischemia is likely in patients with ARF following prolonged or severe renal hypoperfusion complicating hypovolemic or septic shock or major surgery. However, a significant fall in arterial blood pressure occurs in the latter setting in less than half of patients with clinical and biochemical features of ischemic ARF. The likelihood of ischemic ARF is increased further if ARF persists despite restoration of renal perfusion. Diagnosis of nephrotoxic ARF requires review of the history and of pharmacy, nursing, and radiology records for nephrotoxic medications or radiocontrast agents. ARF after cancer chemotherapy suggests a diagnosis of tumor lysis syndrome and acute urate nephropathy, although other considerations include prerenal azotemia due to emesis or diarrhea and direct nephrotoxicity of chemotherapeutic or antimicrobial agents. Rhabdomyolysis is suggested by a recent history of seizures, excessive exercise, alcohol or drug abuse, or muscle tenderness or limb ischemia on physical examination.

While ischemic and nephrotoxic ARF account for most intrinsic renal azotemia, patients should be assessed for other renal parenchymal diseases. Flank pain may be prominant following acute renal artery